## REMARKS

The Examiner rejected claims 1, 2, 4, 6-10, 12, and 14, while withdrawing claims 3, 5, 11, 13, and 15-32 from consideration. Claims 4 and 12 have been amended herein to remove the recitation of SEQ ID NO:3. Claims 9 and 14 have been amended to recite an isolated cell as opposed to a cell. Claims 4, 6, 12, and 14 have been amended to recite moderately or highly stringent hybridization conditions. Applicants specification fully supports these amendments. For example, page 15, lines 16-17 disclose that hybridization conditions can be moderately or highly stringent. Thus, no new matter has been added.

In light of these amendments and the following remarks, Applicants respectfully request reconsideration and allowance of claims 1, 2, 4, 6-10, 12, and 14.

Rejections under 35 U.S.C. § 101

The Examiner rejected claims 1, 2, 4, 6-10, 12, and 14 under 35 U.S.C. § 101 because the claimed invention is allegedly not supported by a specific, substantial and credible asserted utility or a well established utility. The Examiner stated that these claims are directed to SEQ ID NO:1. The Examiner also stated that the invention encompassed by these claims has no apparent or disclosed patentable utility and that the application does not disclose "a specific and substantial biological role of this protein or its significance."

Applicants respectfully disagree. Independent claim 1 recites an isolated nucleic acid molecule that encodes a polypeptide having mu3 opiate receptor activity. Independent claim 6 recites an isolated nucleic acid that hybridizes to the sense or antisense strand of a nucleic acid that encodes a polypeptide having mu3 opiate receptor activity but does not hybridize to the sense or antisense strand of the sequence of human mu1 or mu2 opioid receptors (SEQ ID NO:12 or 13). Independent claim 7 recites an isolated nucleic acid molecule having a nucleic acid sequence with a length and a percent identity to the sequence set forth in SEQ ID NO:1. As disclosed on page 28, lines 7-15 of Applicants' specification, SEQ ID NO:1 contains the new splice variant sequence that makes the 3' portion of mu3 different from the 3' portion of mu1 and mu2. Independent claim 9 recites a cell containing an isolated nucleic acid molecule that

encodes a polypeptide having mu3 opiate receptor activity, while independent claim 14 recites a cell containing an isolated nucleic acid that hybridizes to the sense or antisense strand of a nucleic acid that encodes a polypeptide having mu3 opiate receptor activity but does not hybridize to the sense or antisense strand of the sequence of human mu1 or mu2 opioid receptors. Such nucleic acids and cells containing such nucleic acids have a well established utility.

Mu3 opiate receptors, unlike mu1 and mu2 opioid receptors, were known to have a higher affinity for morphine than for opioid peptides such as DAMGO. See, page 2, lines 20-23 of Applicants' specification; Stefano *et al.*, *Proc. Natl. Acad. Sci.*, 90:11099-103 (1993); and Stefano *et al.*, *Pain Forum*, 8:206-9 (1999). For the Examiner's convenience, copies of these references are provided with the accompanying Information Disclosure Statement. In addition, mu3 opiate receptors were known to be important for controlling pain, inflammation, and immune responses. For example, mu3 opiate receptors were shown to play important roles in regulating immune cell activity, nitric oxide release, and inflammation (Stefano *et al.*, *J. Biol. Chem.*, 270:30290-3 (1995) and Magazine *et al.*, *J. Immunol.*, 156:4845-50 (1996)). Given these well known utilities for mu3 opiate receptors, it is clear that the present claims satisfy the utility requirement of 35 U.S.C. § 101.

In addition, Applicants' specification provides multiple specific, substantial, and credible utilities. For example, the section starting on page 2, line 24 states the following:

> Isolated nucleic acid molecules that encode a polypeptide having mu3 opiate receptor activity, host cells containing such isolated nucleic acid molecules, and substantially pure polypeptides having mu3 opiate receptor activity are particularly useful to research scientists since these materials allow scientists to explore, for example, the interactions of morphine with the mu3 opiate receptor, the molecular mechanisms by which morphine induces intracellular calcium concentration changes, and the relationships of mu3 opiate receptors with other mu opioid receptors. In addition, the methods and materials described herein can be used to provide cells that are responsive to morphine. For example, cells can be transfected with a vector that directs expression of a polypeptide having mu3 opiate receptor activity such that those cells can respond to morphine stimulation.

With respect to the Examiner's comment that "Applicants have not disclosed a full-length mu3 opioid [sic, opiate] receptor polypeptide," Applicants respectfully note that Example 1 discloses cloning the nucleic acid that encodes the human mu3 opiate receptor. The complete open reading frame of the cloned 2.0 kb insert is set forth in SEQ ID NO:4. The 3' portion of SEQ ID NO:4 contains SEQ ID NO:1, the new splice variant sequence that makes the 3' portion of mu3 different from the 3' portion of mu1 and mu2. Upstream sequences of SEQ ID NO:4 are identical to sequences from human mu1 and mu2.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 1, 2, 4, 6-10, 12, and 14 under 35 U.S.C. § 101.

Rejections under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 1, 2, 4, 6-10, 12, and 14 under 35 U.S.C. § 112, as allegedly failing to adequately teach how to use the instant invention. Specifically, the Examiner stated that one skilled in the art clearly would not know how to use the claimed invention since the claimed invention is not supported by a specific, substantial, and credible asserted utility or a well established utility.

Applicants respectfully disagree. As explained above, the presently claimed invention has both a well established utility and an asserted utility that is specific, substantial, and credible. In addition, a person having ordinary skill in the art at the time Applicants filed would have been able to follow the teachings provided throughout Applicants' specification to use the presently claimed invention without undue experimentation. For example, a person having ordinary skill in the art would have been able to transfect cells with a vector that directs expression of a polypeptide having mu3 opiate receptor activity such that those cells can respond to morphine stimulation, thereby allowing those cells to, for example, produce nitric oxide and reduce inflammation. See, e.g., page 2, lines 23-24 and the section from page 2, line 31 to page 3, line 3.

In light of the above, Applicants respectfully request withdrawal of this rejection of claims 1, 2, 4, 6-10, 12, and 14 under 35 U.S.C. § 112, first paragraph.

The Examiner also rejected claims 1, 2, 4, 6-10, 12, and 14 under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for polynucleotides encoding the mu opioid receptors of SEQ ID NO:5, 7, 9 and 11, does not reasonably provide enablement for polynucleotides encoding all mu3 opioid receptors. Specifically, the Examiner alleged that the breadth of the claims is excessive and that Applicants provided only minimal guidance and working example. In addition, the Examiner stated that SEQ ID NO:1 is only 81 nucleotides and it is unclear if it does or does not hybridize to SEQ ID NO:12 and 13. The Examiner also stated that claims reciting a cell comprising the isolated nucleic acid read on gene therapy, requiring Applicants to recite "an isolated cell."

Applicants respectfully disagree. A person having ordinary skill in the art reading Applicants' specification would have been able to make and use the presently claimed invention without undue experimentation. From page 28, lines 7-15 of Applicants' specification, a person having ordinary skill in the art would have understood that the cloned human mu3 opiate receptor is a new splice variant that includes replacing the last 12 amino acid residues of the human mu1 opioid receptor with 26 different amino acid residues. The nucleic acid sequence encoding these new 26 amino acid residues is set forth in SEQ ID NO:1. SEQ ID NO:4 contains the complete open reading frame of the cloned 2.0 kb insert. Thus, SEQ ID NO:4 contains human mu1/mu2 sequence followed by the sequence set forth in SEQ ID NO:1. A person having ordinary skill in the art also would have understood that other nucleic acids encoding a mu3 polypeptide can be obtained without undue experimentation. For example, common PCR cloning techniques similar to those disclosed in Example 1 can be used to obtain mu3 sequences from other species. Moreover, Applicants' specification discloses methods that can be used to determine whether or not a particular polypeptide has mu3 opiate receptor activity. For example, page 22, lines 17-23 discloses that:

> cells expressing a particular polypeptide can be analyzed to determine the polypeptide's binding affinity for morphine and DAMGO. If the binding affinity for morphine is higher than the binding affinity for DAMGO, then the expressed polypeptide has mu3 opiate receptor activity. Controls can be used to confirm the specificity of the various binding affinities. For example, cells lacking the

polypeptide can be used to confirm that the measured binding affinity is specific for that particular polypeptide.

With respect to the Examiner's comments regarding gene therapy, Applicants note that the originally presented claims are fully enabled. To further prosecution, however, claims 9 and 14 have been amended herein to recite an isolated cell as suggested.

In light of the above, Applicants respectfully request withdrawal of this rejection of claims 1, 2, 4, 6-10, 12, and 14 under 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 1, 2, 4, 6-10, 12, and 14 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a was as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner stated that the specification and claims do not indicate what the distinguishing attributes shared by the members of the genus are. The Examiner also stated that the "specification provides a written description of only a partial mu3 opioid [sic, opiate] receptor polynucleotide (SEQ ID NO:1)" and that no other species are described or structurally contemplated within the specification. The Examiner concluded that one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus.

Applicants respectfully disagree. Claim 1 recites an isolated nucleic acid molecule that encodes a polypeptide having mu3 opiate receptor activity. Nucleic acids encoding many different mu1 and mu2 polypeptides were known prior to Applicants' filing date. For example, human, rat, mouse, cow, and pig mu1 sequences were cloned during the 1990s. Applicants' specification discloses cloning mu3, a splice variant of mu1 that includes replacing the last 12 amino acid residues with 26 different amino acid residues. Applicants note that human mu1 is about 400 residues in length. Contrary to the Examiner's statement that the "specification provides a written description of only a partial mu3 opioid [sic, opiate] receptor polynucleotide (SEQ ID NO:1)," Applicants' specification discloses the complete open reading frame of the

cloned 2.0 kb insert and sets that sequence forth in SEQ ID NO:4. In addition, Applicants' specification contemplates and describes additional nucleic acids. For example, page 16, lines 17-21 disclose using common molecular cloning techniques such as site-directed mutagenesis to introduce deletions, insertions, or substitutions into nucleic acid sequences. The section extending from page 29, line 3 to page 31, line 15 discloses nucleic acids combining either human mu1 or human mu2 sequences with the 2.0 kb insert, while the section from page 31, line 16 to page 32, line 19 discloses a chimeric nucleic acid that combines rat mu2 with the human 2.0 kb insert. Moreover, Applicants' specification discloses methods that can be used to determine whether or not a particular polypeptide has mu3 opiate receptor activity. See, e.g., page 22, lines 17-23. Taken together, it is clear that a person having ordinary skill in the art reading Applicants' specification would have appreciated that Applicants invented the presently claimed subject matter. Thus, the present claims are adequately described.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 1, 2, 4, 6-10, 12, and 14 under 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 1, 2, 4, 6-10, 12, and 14 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner stated that the metes and bounds of "activity" are not known. The Examiner also stated that binding a ligand is an activity that would not clearly define the function of or identify "a mu3 opioid [sic, opiate] receptor."

Applicants respectfully disagree. A person having ordinary skill in the art reading Applicants' specification would have understood the meaning of the term "polypeptide having mu3 opiate receptor activity." This is particularly true given that page 2, lines 20-23 of Applicants' specification states that the "term 'mu3 opiate receptor' as used herein refers to a cell surface polypeptide that has a higher affinity for morphine than that for the opioid polypeptide [Tyr-D-Ala$^2$, Gly-N-Me-Phe$^4$, Gly(ol)$^5$]-enkephalin (DAMGO)." In addition, the

next sentence of Applicants' specification states that the "interaction of morphine with a mu3 opiate receptor can induce changes in intracellular calcium concentration and nitric oxide release." Thus, the term "polypeptide having mu3 opiate receptor activity" is clear and unambiguous. Applicants respectfully note that the preferential binding affinity for morphine, instead of opioid peptides including DAMGO, helped demonstrate the existence of the mu3 subtype of mu receptors (Stefano *et al.*, *Proc. Natl. Acad. Sci.*, 90:11099-103 (1993) and Stefano *et al.*, *Pain Forum*, 8:206-9 (1999)).

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 1, 2, 4, 6-10, 12, and 14 under 35 U.S.C. § 112, second paragraph.

The Examiner also rejected claims 4, 6, 12, and 14 under 35 U.S.C. § 112, second paragraph, as being vague and indefinite since the claims recite the word "hybridizes." Specifically, the Examiner stated that it "is not known what these hybridization conditions are," concluding that Applicants are required to amend the claims to recite exact hybridization conditions without using indefinite phrases.

Applicants respectfully disagree. To further prosecution, however, claims 4, 6, 12, and 14 have been amended herein to recite moderately or highly stringent hybridization conditions. Page 15, lines 20-25 define moderately stringent hybridization conditions as follows:

> For the purpose of this invention, moderately stringent hybridization conditions mean the hybridization is performed at about 42°C in a hybridization solution containing 25 mM $KPO_4$ (pH 7.4), 5X SSC, 5X Denhart's solution, 50 μg/mL denatured, sonicated salmon sperm DNA, 50% formamide, 10% Dextran sulfate, and 1-15 ng/mL probe (about $5x10^7$ cpm/μg), while the washes are performed at about 50°C with a wash solution containing 2X SSC and 0.1% sodium dodecyl sulfate.

Page 15, lines 26-31 define highly stringent hybridization conditions as follows:

> Highly stringent hybridization conditions mean the hybridization is performed at about 42°C in a hybridization solution containing 25 mM $KPO_4$ (pH 7.4), 5X SSC, 5X Denhart's solution, 50 μg/mL denatured, sonicated salmon sperm DNA, 50% formamide, 10% Dextran sulfate, and 1-15 ng/mL probe (about $5x10^7$ cpm/μg), while the washes are performed at about 65°C with a wash solution containing 0.2X SSC and 0.1% sodium dodecyl sulfate.

A person having ordinary skill in the art would have understood the meaning of presently amended claims 4, 6, 12, and 14. Thus, the presently claimed invention is clear and unambiguous.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 4, 6, 12, and 14 under 35 U.S.C. § 112, second paragraph.

Rejections under 35 U.S.C. § 102(a)

The Examiner rejected claims 6 and 7 under 35 U.S.C § 102(a) as being anticipated by the Birren *et al.* Accession Number AC027439.

Applicants respectfully disagree. The Birren *et al.* Accession Number AC027439 is a computer record that lists a working draft sequence of human chromosome 6. The note for this record stated the following on November 10, 2004:

> This is a "working draft" sequence. It currently consists of 18 contigs. The true order of the pieces is not known and their order in this sequence record is arbitrary. Gaps between the contigs are represented as runs of N, but the exact sizes of the gaps are unknown. This record will be updated with the finished sequence as soon as it is available and the accession number will be preserved.

Claims 6 and 7 recite isolated nucleic acid molecules. Page 7, lines 7-10 of Applicants' specification state that the "term 'isolated' as used herein with reference to nucleic acid refers to a naturally-occurring nucleic acid that is not immediately contiguous with both of the sequences with which it is immediately contiguous (one on the 5' end and one on the 3' end) in the naturally-occurring genome of the organism from which it is derived." None of the 18 contigs listed in the Birren *et al.* computer record is an isolated nucleic acid as presently claimed. Applicants note that the sequence of SEQ ID NO:1 was found at nucleotides 33444 to 33524 of the working draft sequence.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 6 and 7 under 35 U.S.C. § 102(a).

Rejections under 35 U.S.C. § 103(a)

The Examiner rejected claim 14 under 35 U.S.C § 103(a) as being unpatentable over the Birren *et al.* Accession Number AC027439 in view of the Sibson *et al.* reference (WO 95/01548). Specifically, the Examiner stated that it "would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the invention of Sibson et al. by substituting a cDNA in the polycloning region of the vector with the polynucleotide (cDNA) of Birren et al. for the purpose of transfecting a host cell as taught by Sibson et al. in view of Sibson's et al.'s suggestion that it would be desirable to do so (pages 8-13)."

Applicants respectfully disagree. The nucleic acid sequence listed in the Birren *et al.* computer record is not a cDNA. It is a working draft sequence of human chromosome 6 that is 182,048 nucleotides long. The Sibson *et al.* reference provides no information about mu3 opiate receptor polypeptides or sequences encoding such polypeptides. A person having ordinary skill in the art reading these cited references would not have been motivated to insert a working draft sequence 182,048 nucleotides long into a vector for the purpose of transfecting a host cell. Thus, the cited references do not render claim 14 obvious.

In light of the above, Applicants respectfully request withdrawal of the rejection of claim 14 under 35 U.S.C. § 103(a).

## CONCLUSION

Applicants submit that claims 1, 2, 4, 6-10, 12, and 14 are in condition for allowance, which action is requested. The Examiner is invited to call the undersigned attorney at the

telephone number below if such will advance prosecution of this application. The Commissioner is authorized to charge any fees or credit any overpayments to Deposit Account No. 06-1050.

Respectfully submitted,

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